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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/764,390

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Arthur B. Raitano

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MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER

CANELLA, KAREN A

ART UNIT

PAPER NUMBER

1643

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/764,390	Applicant(s) RAITANO ET AL.	
	Examiner Karen A. Canella	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 49,54-63,66,72,75,77,79 and 80 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) 49,54-63,66,72,75,77,79 and 80 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>5/48/2006 4/26/205</u> | 6) <input type="checkbox"/> Other: ____ |

KAC
Corrected

DETAILED ACTION

1. Claims 50-53, 64, 65, 67-71, 73, 74, 76 and 78 have been canceled. Claims 49, 54-58, 60-62, 66, 72, 75 and 77 have been amended. Claims 79 and 80 have been added. Claims 49, 54-63, 66, 72, 75, 77, 79 and 80 are pending and under consideration.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. Claim 55 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention..

It is unclear how claim 55 further modifies claim 54. Claim 54 requires a fragment of a polypeptide which induces a specific antibody response. Claim 55 specifies that said fragment comprises one or more immunoreactive epitopes. The presence of one or more immunoreactive epitopes would be inherent in claim 54, therefore it is unclear how claim 55 further limits the scope of claim 54.

4. Claims 49, 54-63, 66, 72, 75, 77, 79 and 80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

(A)As drawn to SEQ ID NO:3, 5 and 7, and a method of detecting the presence of cancer in an individual.

Claims 49 and 57 are drawn to an isolated or recombinant polypeptide comprising SEQ ID NO:3, 5 or 7, and composition thereof. Claims 75 and 77 are drawn to a method of detecting cancer in a patient comprising determining the expression level of a polypeptide comprising SEQ ID NO:3, 5 or 7. The specification asserts that 254P1D6B can be used in the same manner as other tumor antigens such as PSA, because 254P1D6B is expressed in lung, ovary, prostate, pancreas and breast tissues, when said tissues are malignant (page 122). The specification sets

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forth the polynucleotide of 254P1D6B v.1 clone LCP-3 as encoding SEQ ID NO:3 (Figure 2A); polynucleotides of 254P1D6B v.2 as encoding SEQ ID NO:5 (Figure 2B) and 254P1D6B v.3 as encoding SEQ ID NO:7 (Figure 2C). The specification fails to provide a nexus between the expression of 254P1D6B in cancerous lung, ovary, prostate, pancreas and breast and the expression of the individual variant sequences. It is further noted that claim 75 is broadly drawn to accommodate all cancers, rather than the specific cancer listed on page 12 of the specification. When given the broadest reasonable interpretation the term “cancer” includes malignancies from other cell types than those listed on page 122 and in addition includes sarcomas, neuroblastoma, melanomas, leukemias and lymphomas, etc. The scope of the claims must be commensurate with the scope of the enablement set forth. One of skill in the art would be forced into determining if the expression pattern of the claimed variant polynucleotides were the same as that which is set forth for 254P1D6B before being able to use said variants as markers for the detection of the described cancers on page 122, and would be subject to an even greater degree of undue experimentation in order to determine if the polynucleotides of SEQ ID NO:3, 5 and 7 were over expressed in cancers other than those listed on page 122 in order to practice the claimed method to the full scope.. There is no objective evidence that all the variants possess the same properties as that reported for the “generic” 254P1D6B sequence and there is no objective evidence that the “generic” 254P1D6B sequence is over expressed in cancers from various malignancies such as sarcomas, melanomas and neuroblastoma, etc. .

(B)As drawn to a method of generating an immune response.

Claims 58-62, 79 and 80 are drawn to a method of generating an immune response in a mammal comprising exposing cells of said mammal to a polypeptide comprising SEQ ID NO:3, 5 or 7 and encompasses the generation of cytotoxic T cells which kill autologous cells which express said proteins. The specification asserts that 254P1D6B is a target for antibody based therapy and contemplates that the antibodies can be used to evoke complement and ADCC-mediated cell killing (page 49). However, it is well known in the art that the antibody must bind to the cell surface in order to evoke complement lysis or ADCC (Abbas et al, “Cellular and Molecular Immunology”, 1991, pages 57-58) and there is no evidence in the specification that said 254P1D6B protein is a cell surface protein. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the claimed method of

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generating an immune response wherein said immune response were complement-mediated killing or ADCC. The specification also asserts that intracellular molecules can be targeted by intrabodies. However the specification is not enabled for the making and using of intrabodies for the targeting of the 254P1D6 protein. The art recognizes that in order to provide "intrabodies" it is necessary to know the minimum sequence of an antigen binding portion of an antibody which binds to the protein being targeted (Jones et al., *Advanced Drug Delivery Reviews* 1998, page 154, column 1, lines 18-26, and page 160, lines 24-25). In the instant case no sequence of an antibody has been provided.

The specification asserts that 254P1D6B is a target for cellular immune responses (page 52 and section X.C.). However, the art teaches that the induction of a cellular immune response against a tumor antigen is unreliable. The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, *Fundamental Immunology*, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4). Paul teaches that lymphocytes from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors"). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors", page 1167). With respect to the blocking factor found in serum, Apostolopoulos et al (*Nature Medicine*, 1998, vol. 4, pp. 315-320) teach that endogenous antibodies present at the time of administration of a tumor peptide re-routes the immune response from a cellular response to a humoral response. In preclinical

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experiments with mice, MUC1 peptides targeted to the mannose receptor produce high levels of CTL and a low level of antibodies. However, in human clinical trials a low level of CTL and a high level of humoral response was observed (Apostolopoulos, page 315, first column, bridging paragraph). Apostolopoulos et al teach that the presence of endogenous antibodies which bind to the MUC1 peptide was responsible for this re-routing of the immune response from cellular to humoral due to the Fc portion of the antibody (page 319, first column, lines 7-10).

Apostolopoulos et al teach that mice are devoid of these antibodies (page 315, second column, lines 9-13) and are thus able to effectively mount a cellular immune response against the target antigen. Apostolopoulos et al teach that these findings have implication for other immunotherapy approaches (page 318, lines 4-8, under the heading "Discussion". In support of these conclusions Jager et al (PNAS, 2000, Vol. 97, pp. 12198-12203) teach that patients who do not have antibodies to the cancer testis antigen, NY-ESO-1, were able to generate a specific T-cell response to NY-ESO after intradermal administration, whereas patients having antibodies prior to treatment which reacted with said antigen already had T-cells which reacted with target cells expressing said antigen in vitro, and said positive patients did not develop significant CTL in response to the administered NY-ESO antigen. These references serve to demonstrate that the induction of a anti-tumor CTL response after the administration of a tumor peptide is unpredictable.

Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstract of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105 and the abstract of Algarra et al International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. The effect of the claimed method upon such a heterogeneous tumor has not been demonstrated by the specification. More currently, the abstract of Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teaches that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules.

Sarma et al (Journal of Experimental Medicine, 1999, Vol. 189, pp. 811-820) states that a critical issue in therapeutic regiments comprising the administration of tumor antigens for immunotherapy is whether unmutated tumor antigens which are expressed in normal cells impose special restrictions on the CTL response in vivo. Using transgenic mice wherein the antigen specific T cells specific for the P1A non-mutated tumor antigen are expressed at high levels and remain responsive to the P1A antigen when assayed in vitro, it was found that P1A antigen expressed in the thymus resulted in clonal deletion of said specific T-cells. Sarma et al note that although said transgenic mice produce an overwhelming majority of T cells that are specific for P1A, said mice are no more resistant to cells expressing P1A than non-transgenic litter mates. Sarma et al concludes that even though P1A can be a tumor rejection antigen, the effector function of P1A specific CTL is restrained in vivo and that these results have important implications for the strategy of tumor immunotherapy. The specification asserts that the instant tumor antigen is akin to PSA, but does not provide evidence that the 254P1DB protein is a self protein which is differentially up regulated in cancer cells or a mutated protein. Following the pattern of PSA as suggested by the specification would lead to the conclusion that the 254P1DB protein is a self protein which is differentially up regulated in cancer cells and subject to the difficulties associated with a self antigen as those discussed by Sarma above.

It is also well known that the presence or induction of CTL which can lyse target cells in vitro has no apparent nexus with anti-tumor cytolytic activity in vivo. Ohlen et al (Journal of Immunology, 2001, Vol.166, pp. 2863-2870) teach that T-cells recognizing normal proteins expressed in tumors can be isolated in vitro, but that the existence of said T-cells does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995, Vol. 7, pp. 715-725) teach that T-cells which are impaired in the ability to proliferate in response to antigen and unable to reject tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). These references serve to demonstrate that the induction of a CTL response against the 254P1DB protein ex vivo or in vitro does not constitute evidence that said T-lymphocytes would be effective at lysing tumor cells in vivo or functioning in immunotherapy in a patient in need thereof.

Further, it is recognized in the art that animal models for immunotherapy are deficient. Schultze et al (Trends in Immunology, 2004, Vol. 25, pp 659-664) teach that encouraging animal model studies lead to clinical trials, but that the general outcomes of these trials are disappointing, citing a discrepancy between the outcome of pre-clinical models and the outcome of the human situation. Bodey et al, (Anticancer Research, 2000, Vol. 20, pp. 2665-2676) teach that the animal models often produce highly encouraging results but that the resulting response in humans is disappointing

It is concluded based on the references discussed above, that the state of the art with respect to treating patients with cancer by means of administering tumor antigens is unpredictable. The specification does not provide any disclosure that the administration of the claimed polypeptides would generate CTLs which lyse the cells of a tumor in situ, and it cannot be predicted based on the prediction of HLA-binding motifs that said polypeptides would be useful in immunotherapy in patients. Thus, without a demonstration that the administration of the claimed polypeptides or cells expressing said polypeptides overcomes immunosuppression of the host, the rapid growth of the target tumor cells, failure to access the tumor because of the stromal barrier and tolerance induction in the host and objective evidence that the target tumor cells in vivo present adequate tumor rejection antigen on the surface of all the tumor cells, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the claimed method of treatment and the claimed polypeptides.

(C)As drawn to fragments of SEQ ID NO:3, 5 and 7.

Claim 54 is drawn to a fragment of SEQ ID NO:3, 5 or 7, wherein said fragment induces a specific antibody response. Claim 55 embodies the method of claim 54 wherein said fragment comprises one or more immunoreactive epitopes. The specification asserts that HLA binding fragments were determined by computer search algorithms (page 93, under Example 13). The art Burch (WO 03/084467, page 5, lines 18-21) teaches that the vast majority of predicted HLA epitopes fail to be immunogenic. One of skill in the art would be subject to undue experimentation in order to test the multitude of epitopes on pages 136-196 for immunogenicity

(D)As drawn to the expression analysis of 254P1D6B and the individual sequences of SEQ ID NO:2, 4 or 6.

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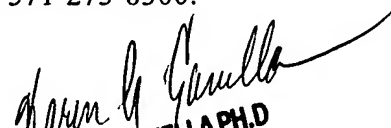
Claims 63, 66 and 72 are drawn to the polynucleotides encoding the polypeptides of SEQ ID NO:3, 5 or 7, full complements thereof; and polynucleotides comprising SEQ ID NO:2, 4 and 6. The polynucleotides sequences are rejected for the same reasons as applied to the polypeptides in section (A) above.

5. Claims 54-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 54 has been amended to recite wherein the fragment consists of nine, ten or fifteen contiguous amino acids of the polypeptide of claim 49, and wherein said fragment induces a specific antibody response. It is noted that the tables on pages 136-196 provide numerous examples of fragment having nine, ten or fifteen contiguous amino acids of the polypeptides of claim 49, however, the specification lacks specific support for this limitation in combination with the induction of a specific antibody response. One of skill in the art would reasonable conclude that applicant was not in possession of the claimed genus of fragments.

6. All other rejections and objections are withdrawn in light of applicants amendments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



KAREN A. CANELLA PH.D.
PRIMARY EXAMINER

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Karen A. Canella, Ph.D.

7/24/2006


KAREN A. CANELLA PH.D.
PRIMARY EXAMINER